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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/461,090	12/14/1999	AXEL ULLRICH	2923-0347	3321

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EXAMINER

LU, FRANK WEI MIN

ART UNIT	PAPER NUMBER
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1634

DATE MAILED: 03/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/461,090

Applicant(s)

ULLRICH ET AL.

Examiner

Frank W Lu

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 November 2003.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 22-31 and 33-37 is/are pending in the application.
- 4a) Of the above claim(s) 37 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 22-31 and 33-36 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

Continued Examination

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 25, 2003 has been entered. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of applicant's amendment filed on November 25, 2003. The claims pending in this application are claims 22-31 and 33-37. Since claims 22-31 and 33-36 that were rejected in final office action do not have a first cell and a second cell and do not require that the first cell is in contact with the second cell, newly added claim 37, which has a first cell and a second cell and require that the first cell is in contact with the second cell, is considered as an independent or distinct from the invention originally claimed. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 37 has been withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. Therefore, claim 37 will not include this office action and claims 22-31 and 33-36 will be examined.

Claim Objections

2. Claims 22 and 36 are objected to because of the following informality: "resulting in" should be "and resulting in".
3. Claim 24 is objected to because of the following informalities: (1) "(I)" should be "(i)"; and (2) "said compound affecting an extracellular G protein or G protein coupled receptor initiated signal pathway" should be "said compound affecting G protein or G protein coupled receptor initiated extracellular signal pathway" in order to correspond to claim 22.
4. Claims 26 and 27 are objected to because of the following informality: "said precursor of a ligand" should be "said precursor of the ligand".
5. Claim 33 is objected to because of the following informalities: (1) EGFR", HER, TNF, CD, IL are abbreviations. They can only be used after each abbreviation appears once; and (2) "AND" should be "and".
6. Claim 35 is objected to because of the following informality: "compounds" in preamble should be "a test compound" in order to correspond to "a test compound" in the content of the claim.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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8. Claims 22-31, 33, 34, and 36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Although the specification describes G protein mediated signal transduction and G-protein-coupled receptors (see specification, page 1), the specification does not adequately describe that G protein coupled receptor initiated extracellular signal pathway recited in claims 22-31, 33, 34, and 36. MPEP 2163.06 states that "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." In view of the embodiments adequately description in the specification, the subject application does not reasonably convey to one skilled in the art that applicant was in possession of the full scopes of products encompass in the claims at the time of the application was filled. Therefore, the written description requirement has not been satisfied.

In support of this position, attention is directed to the decision of *Vas-Cath inc. V.*

Mahurkar 19 USPQ2d 1111 (CAFC, 1991):

This court in *Wilder* (and the CCPA before it) clearly recognized, and we hereby reaffirm, that 35 U.S.C. 112, first paragraph, requires a "written description of the invention" which is separate and distinct from the enablement requirement. The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the "applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*. The following is a quotation of the second paragraph of 35 U.S.C. 112:

9.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 22-31 and 33-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
11. Claims 22 and 36 are rejected as vague and indefinite. Since it is known that stimulation of G protein mediated signal transduction can result in an activation of a receptor tyrosine kinase, it is unclear that "stimulating" step or "contacting" step are the same method step or different method steps. Furthermore, since disturbing G protein mediated signal transduction may result in inactivation of the receptor tyrosine kinase, the first part and second part of claims 22 and 26 do not correspond each other. Please clarify.
12. Claim 35 is rejected as vague and indefinite. Although the claim is directed to a method for identifying compounds for modulating G-protein mediated signal transduction, there is no method step for identify compounds for modulating G-protein mediated signal transduction and the goal of the method (preamble) does not match with the method steps of the claim. Please clarify.
13. Claim 36 is rejected as vague and indefinite in view of "said cell comprising an extracellular domain" because it is unclear that said cell comprises an extracellular domain from which protein. Please clarify.
14. Claim 36 is rejected as vague and indefinite in view of "based on the activation of signal transduction pathway" because it is unclear that "signal transduction pathway" in this phrase is identical to "G protein mediated signal transduction" in the first line of the claim or not. Please clarify.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

16. Claims 22-26, 28-31, and 33-36 are rejected under 35 U.S.C. 102(a) as being anticipated by Dong *et al.*, (Proc. Natl. Acad. Sci. USA, 96, 6235-6240, May 1999).

Dong *et al.*, teach metalloprotease-mediated ligand release regulates autocrine signaling through the epidermal growth factor receptor.

Regarding claims 22, 23, 33, and 34, since Dong *et al.*, teach to treat HMEC cells with batimastat, antagonist mAb225 or EGF (see page 6238, right column and Figure 4) and there is no evidence to show that batimastat can not affect a G protein or G protein coupled receptor initiated extracellular signal pathway, Dong *et al.*, disclose contacting a cell with a compound (ie., batimastat) affecting a G protein or G protein coupled receptor initiated extracellular signal pathway as recited in claim 22. Since Dong *et al.*, teach that batimastat +EGF increase the level of EGFR tyrosine phosphorylation (see page 6238, right column and Figure 4) and it is known that increased level of EGFR tyrosine phosphorylation in a cell indicates that a G protein or G protein coupled receptor initiated extracellular signal pathway of the cell has been activated (for evidence, see claim 36 of this instant application), Dong *et al.*, disclose stimulating G protein mediated signal transduction in a cell (ie., treating HMEC cells with batimastat+EGF) having a receptor tyrosine kinase (ie., EGFR) capable of activation by G-protein mediated signal

transduction or contacting a cell with a compound (ie., batimastat in the presence of EGF) affecting a G protein or G protein coupled receptor initiated extracellular signal pathway so that resulting in an activation of the receptor tyrosine kinase (ie., increasing the level of EGFR tyrosine phosphorylation) and thereby modulating the receptor tyrosine kinase activation by G-protein-mediated signal transduction (ie., increasing the level of EGFR tyrosine phosphorylation) as recited in claim 22 wherein said tyrosine kinase is EGFR as recited in claims 23, 33, and 34.

Regarding claims 24-26 and 28-31, since Dong *et al.*, teach that ligands such as EGF that activate the epidermal growth factor receptor (EGFR) are synthesized as membrane-anchored precursors that are proteolytically released by members of the ADAM family of metalloproteinases and batimastat is a metalloproteinase inhibitor that prevents EGFR ligand such as EGF release by abolish biological activity of the metalloproteinases (see page 6235, abstract and right column, and page 6239, right column, last paragraph), Dong *et al.*, disclose said compound (ie., batimastat) affecting the G protein or the G protein coupled receptor initiated extracellular signal pathway affects a proteinase (ie., a metalloproteinase) cleaving a precursor of a ligand (ie., the precursor of EGF) for the receptor tyrosine kinase (ie., EGFR) as recited in claim 24 wherein the compound (ie., batimastat) affects the proteinase (ie., metalloproteinase) by directly inhibiting proteinase activity as recited in claim 25, wherein said precursor of a ligand (ie., the precursor of EGF) is a membrane associated molecule as recited in claim 26, wherein said proteinase is a metalloproteinase as recited in claim 29, and said proteinase activity (ie., biological activity of the metalloproteinase) is inhibited by batimastat as recited in claim 31. Since Dong *et al.*, teach that EGF is proteolytically released from its membrane-anchored precursor by members of the

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ADAM family of metalloproteases (see page 6235, abstract) and it is known that the ADAM family of metalloproteases are zinc-dependent proteinases (see the specification, page 3, first paragraph), Dong *et al.*, disclose said proteinase (ie., one of the ADAM family of metalloproteases taught by Dong *et al.*,) is a membrane-associated proteinase as recited in claim 28 and said metalloprotease (ie., one of the ADAM family of metalloproteases taught by Dong *et al.*,) is a zinc-dependent proteinase as recited in claim 30.

Regarding claim 35, since Dong *et al.*, teach to treat HMEC cells comprising EGFR with batimastat, antagonist mAb225 or EGF wherein batimastat +EGF increase the level of EGFR tyrosine phosphorylation (see page 6238, right column and Figure 4) and it is known that increased level of EGFR tyrosine phosphorylation in a cell indicates that a G protein or G protein coupled receptor initiated extracellular signal pathway of the cell has been activated (for evidence, see claim 36 of this instant application), Dong *et al.*, disclose contacting a cell containing a receptor tyrosine kinase (ie., a HMEC cell) capable of activation by G-protein mediated signal transduction with a test compound (ie., batimastat) as recited in the claim. Since Dong *et al.*, teach that batimastat is a selective metalloprotease inhibitor that prevents EGFR ligand release (see page 6235, abstract and right column, and page 6239, right column, last paragraph) and there is no evidence to show that batimastat can not affect a G protein or G protein coupled receptor initiated extracellular signal pathway, Dong *et al.*, disclose a test compound suspected of being a modulator (ie., batimastat) of a proteinase (ie., a selective metalloprotease) or a precursor of a ligand (ie., the precursor of EGF) of the receptor tyrosine kinase (ie., EGFR) as recited in the claim. Since Dong *et al.*, teach to compare the level of EGFR tyrosine phosphorylation of HMEC in the presence of batimastat, antagonist mAb225 or

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EGF (see Figure 4), Dong *et al.*, disclose evaluating G-protein mediated receptor tyrosine kinase (ie., EGFR) activation upon exposure of the cell (ie., HMEC) to said test compound (ie., batimastat) as recited in the claim.

Regarding claim 36, since Dong *et al.*, teach to treat HMEC cells with batimastat, antagonist mAb225 or EGF (see page 6238, right column and Figure 4) and there is no evidence to show that batimastat can not affect a G protein or G protein coupled receptor initiated extracellular signal pathway, Dong *et al.*, disclose contacting a cell with a compound (ie., batimastat) affecting a G protein or G protein coupled receptor initiated extracellular signal pathway as recited in the claim. Since Dong *et al.*, teach that batimastat +EGF increase the level of EGFR tyrosine phosphorylation (see page 6238, right column and Figure 4) and it is known that increased level of EGFR tyrosine phosphorylation in a cell indicates that a G protein or G protein coupled receptor initiated extracellular signal pathway of the cell has been activated (for evidence, see claim 36 of this instant application), Dong *et al.*, disclose stimulating G protein mediated signal transduction in a cell (ie., treating HMEC cells with batimastat+EGF) having a receptor tyrosine kinase (ie., EGFR) capable of activation by G-protein mediated signal transduction or contacting a cell with a compound (ie., batimastat in the presence of EGF) affecting a G protein or G protein coupled receptor initiated extracellular signal pathway so that resulting in an activation of the receptor tyrosine kinase (ie., increasing the level of EGFR tyrosine phosphorylation) and thereby modulating the receptor tyrosine kinase activation by G-protein-mediated signal transduction (ie., increasing the level of EGFR tyrosine phosphorylation) wherein said tyrosine kinase is EGFR as recited in the claim. Since it is known that EGFR has an extracellular domain and a cell comprising EGFR has a G-protein mediated

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signal transduction pathway wherein EGFR activation occurs by tyrosine phosphorylation of EGFR (see the specification, page 1, last paragraph, and page 2, second paragraph), Dong *et al.*, disclose said receptor tyrosine kinase is EGFR and said cell (ie., HMEC) comprising the extracellular domain of EGFR and having a G-protein mediated signal transduction pathway wherein one or more tyrosine residues are phosphorylated based on the activation of signal transduction pathway as recited in the claim. Since Dong *et al.*, teach that EGF is generated from its membrane-anchored precursor by one of the ADAM family of metalloproteases (see page 6235, abstract) and it is known that EGF binds to the extracellular domain of EGFR, Dong *et al.*, disclose that the extracellular domain of said receptor (ie., EGFR) is capable of binding to its receptor ligand (ie., EGF) and said ligand is generated from a precursor of said ligand (ie., the precursor of EGF) by a proteinase-dependent cleavage (ie., one of the ADAM family of metalloproteases) as recited in the claim.

Therefore, Dong *et al.*, teach all limitations recited in claims 22-26, 28-31, and 33-36.

Response to Arguments

In page 8, second paragraph of applicant's remarks, applicant argues that "the statement of page 5, lines 4-8 of the office action, that Dong used batimastat to study the effect of EGFR on G-protein mediated signal transduction pathways is incorrect. Dong does not reference the G protein and discusses only the inhibition of autocrine signal transduction by means of EGFR."

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, the invention of this instant application and Dong *et al.*, use the same metalloprotease inhibitor, batimastat in their methods. Since identical compound (ie., batimastat) must have an identical effect on the G-protein mediated signal transduction pathway

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and must follow the same mechanism, Dong *et al.*, teach to use batimastat to study the effect of EGFR on G-protein mediated signal transduction pathways. Second, Dong *et al.*, do indirectly reference the G protein since they teach EGFR tyrosine phosphorylation. Note that it is known that increased level of EGFR tyrosine phosphorylation in a cell indicates that a G protein or G protein coupled receptor initiated extracellular signal pathway of the cell has been activated (for evidence, see claim 36 of this instant application).

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dong *et al.*, (May, 1999) as applied to claims 22-26, 28-31, and 33-36 above, and further in view of Miyoshi *et al.*, (J. Biol. Chem., 272, 14349-14355, 1997).

The teachings of Dong *et al.*, have been summarized previously, *supra*.

Dong *et al.*, do not disclose that said precursor of the ligand for the receptor tyrosine kinase is proHB-EGF as recited in claim 27. .

Miyoshi *et al.*, do teach a cell line, AH66tc, that can produce proHB-EGF and contains EGFR (see abstract in page 14349, right column in page 14351, and Figure 4 in page 14352).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have used AH66tc to perform the method recited in claim 22 in view of the references of Dong *et al.*, and Miyoshi *et al.*, so that HB-EGF released from pro-HB-EGF can activate EGFR by binding to its extracellular domain. One having ordinary skill in the art would have been motivated to do so because the simple replacement of one kind of cell line that is capable to produce a ligand of EGFR (ie., a human mammary epithelial cell line that can produce EGF taught by Dong *et al.*,) from another kind of cell line that is capable to produce a ligand of EGFR (ie., AH66tc that can produce HB-EGF taught by Miyoshi *et al.*,) during the process of performing the method recited in claim 22 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the replacement would not change the method steps of claim 22 since it is known that a variety of ligands such as HB-EGF in addition to EGF have been shown to stimulate EGFR and is released from their membrane-anchored precursors (see Dong *et al.*, page 6235, left column).

Furthermore, the motivation to make the substitution cited above arises from the

expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements in such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Conclusion

19. No claim is allowed.
20. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571)272-0782.

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Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.



Frank Lu

PSA

March 5, 2004

FRANK LU
PATENT EXAMINER